Amendment to the Drawing

The attached sheets of Drawings include new Figures 5-9, which correspond to Figures 1-5 of U.S.S.N. 09/141,220 that have been incorporated into the present application by reference. Upon incorporation, the numbering of Figures 1-5 of U.S.S.N. 09/141,220 has been amended to Figures 5-9 in order to maintain continuity with Figures 1-4 of the present application. Incorporated Figures 5-9 are attached hereto. Applicant submits that no new matter has been added by the present Amendment to the Drawing.

Attachment: Replacement Sheets

Remarks

Applicant submits that no new matter has been added by the present Amendment. Applicant respectfully requests reexamination and reconsideration of the case in light of the present Amendment and the following Remarks. Each of the rejections levied in the Office Action is addressed individually below.

Interview

Applicant thanks the Examiner and her Supervisor for an in-person interview that took place on August 27, 2007, at which the present rejections were discussed. The Examiner suggested claim Amendments and indicated that these will obviate the enablement and written description rejections under 35 U.S.C. § 112 once the material incorporated by reference to U.S. Serial No. 09/141,220 is introduced into the application. The Examiner and the Applicant also discussed the obviousness rejections under § 103.

Amendments to the specification

The specification has been amended to include material incorporated by reference from U.S. Serial No. 09/141,220 (the '220 application). The '220 application was filed by Applicant in 1998 and describes the modification of the peanut allergens Ara h 1, 2 and 3. The '220 application (including all Tables, Examples, written description, and Sequence Listing) was incorporated by reference in its entirety on page 20, line 29 to page 21, line 1 of the present application as originally filed to provide explicit description of modified peanut allergens with reduced IgE binding. The Examiner has acknowledged that the specification can properly be amended to include material incorporated by reference. As requested by the Examiner, Applicant has amended the specification to include material that is incorporated by reference from the '220 application. Applicant respectfully submits that no new matter is added in light of the proper incorporation by reference.

Please note that Figures 1-5 and Examples 1-5 of the '220 application were renumbered as Figures 5-9 and Examples 5-9 upon incorporation into the present specification in order to maintain continuity of numbering of the Figures and Examples. Thus, Figures 5-9 and Examples

5-9 of the presently amended specification correspond to Figures 1-5 and Examples 1-5, respectively, of the '220 application.

Please note that SEQ ID NOs: 1-3 as originally presented in the present case have been renumbered as SEQ ID NOs: 81-83 in order to maintain continuity of numbering of SEQ ID NOs. Thus, SEQ ID NOs: 81-83 of the presently amended specification correspond to SEQ ID NOs: 1-3, respectively, of the present application as originally filed.

Status of the claims

Claims 34-47 are pending in the application. Claim 37 has been withdrawn from consideration, claims 1-33 are canceled, and new claims 48 and 49 have been added. Claims 34-36 and 38-47 stand rejected. Claim 1 has been amended for clarity. Claim 39 has been amended to correct the antecedent basis of that claim. Support for new claims 48 and 49 can be found in the present specification, for example, on page 29, lines 24-26; and page 30, lines 26-29. Applicant submits that no new matter has been added by the present Amendment to the Claims.

Rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement and written description

The Examiner has rejected claims 34-36 and 38-47 for alleged lack of enablement and written description. As discussed during the interview between the Examiner and the Applicant, the present specification, including the material incorporated by reference to U.S.S.N. 09/141,220 (the '220 application), provides enablement and written description for the claims. For all of the reasons previously set forth and those discussed in the interview, the rejection under 35 U.S.C. § 112, first paragraph should be removed.

For example, Applicant points out that the present specification includes the entire sequence of each of the wild type peanut allergens referred to in the claims (see, for example, SEQ ID NOs.: 2, 4, and 6); the specification also identifies or refers to the *known* IgE epitopes of each of these allergens (Tables 1-3 of the present specification). The specification also describes specific modifications of many of these IgE epitopes that reduce IgE binding (Tables 4-6 of the present specification). It is true that the specification does not specifically exemplify every possible mutation of every IgE epitope that can reduce IgE binding or cross-linking activity. However, as discussed during the interview, in light of the power of Molecular Biology, it is well within the purview of the person of ordinary skill to make other changes within these *precisely*

defined sequences and to test them to assess their effects on IgE binding or cross-linking. Such work is routine, even if laborious. Certainly, it the experimentation it requires is no more *undue* than that required in *In re Wands*, the legal standard for enablement.

Furthermore, the specification includes an appendix including an extensive list of various wild type allergens of many different types (*e.g.*, weed pollens, grass pollens, tree pollens, mites, animals, fungi, insects, foods, among others). All of the listed allergens (~325 different allergens) include either GenBank accession numbers or references to published literature that describe these sequences. As discussed during the Interview, one of ordinary skill in the art reading the specification would easily be able to apply the methods and principles explicitly exemplified in the specification to any of the ~325 allergens in the appendix.

In addition, as discussed above, the specification goes into great detail characterizing three of these allergens (*i.e.*, Ara h 1, Ara h 2, and Ara h 3). Although these three proteins are all peanut allergens with names that sound similar to one another, they are in fact very different proteins with different amino acid sequences (SEQ ID NOs: 2, 4, and 6). Thus, the specification describes and reduces to practice compositions and methods relating to *three distinct* proteins. For all of these reasons, Applicant respectfully submits that the specification is enabling and fully descriptive for *any* allergen.

As agreed upon by the Applicant, Examiner, and her Supervisor, Applicant respectfully submits that the claims are enabled by and are fully described in the specification. Applicant, therefore, respectfully requests that the rejections under § 112, first paragraph, for alleged lack of enablement and written description be removed.

Rejection under 35 U.S.C. § 112, second paragraph, as being indefinite

Claims 34-36 and 39-40 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner states that the recitation of "wild-type allergen that occurs in nature" in claim 34 is ambiguous and indefinite. Applicant respectfully disagrees.

The term "wild type" is well understood in the art. Indeed, the established USPTO practice confirms the definiteness of the term. For example, a search of the USPTO's database reveals 2,339 different issued patents that recite "wild type" in the claims (the first page of the search results are attached as Appendix A). Even a cursory review of these results shows that the term "wild type" is recited extensively in claims that have been issued by the USPTO. The

specifications of these patents typically do not provide any definition of the term "wild type," and certainly do not usually link the term to any specific amino acid or nucleotide sequence. For example, please find attached in Appendix A a few issued U.S. patents identified in the search (*i.e.*, 7,335,471; 7,335,363; 7,332,174; and 7,323,303), which are just a few examples of issued patents with claims that recite "wild type," but do not define "wild type" in the claims or specification as having a particular amino acid or nucleotide sequence. Applicant respectfully submits that this analysis reveals that the USPTO appreciates that the term "wild type" is readily understood by one of ordinary skill in the art and is not indefinite. Therefore, the present claims, which recite a "wild type allergen," are not indefinite under § 112, and Applicant respectfully requests that the rejection be removed.

The Examiner states that "wild-type *peanut* allergen" in claim 39, line 3 has no antecedent basis in claim 34. Applicant thanks the Examiner for pointing out this inadvertent error and has amended claim 39 to remove the word "peanut." Applicant respectfully submits that the rejection is rendered moot by the present Amendment.

Rejections under 35 U.S.C § 103(a) for obviousness

The Examiner has rejected claims 34-40, 42, and 43 under 35 U.S.C. § 103 as being unpatentable over WO 99/38978 ("the '978 publication") in view of Fenton *et al.* (1995, *J. Natl. Cancer Inst.*, 87(24):1853-1861) and Vrtala *et al.* (1995, *Int. Arch. Allergy Immunol.*, 107:290-294). This rejection is respectfully traversed; reconsideration and withdrawal is requested.

The Examiner states that the '978 publication "teaches a composition comprising *E. coli* comprising at least one recombinant modified allergen such as modified peanut allergen Ara h1, Ara h2, and Ara h3" (page 20 of the Office Action). The Examiner goes on to state that "The reference modified peanut allergen is encapsulated inside the dead *E. coli* because the recombinant modified protein is expressed in inclusion bodies which located [*sic*] in the cytoplasm since it must be solubilized with urea" (page 20 of the Office Action). Applicant respectfully disagrees with the Examiner's interpretation of the teachings of the '978 publication.

The Examiner points to a particular portion of the '978 publication (page 16, lines 22-33) as describing modified allergens expressed in *E. coli*. However, this is not a correct interpretation of that portion of the '978 description. The disclosure on page 16, lines 22-33 of

the '978 publication describes expression of a *wild type* allergen (*i.e.,* Ara h 2). This wild type allergen is used for screening pooled serum to identify patient populations expressing antibodies that recognize the expressed wild type allergen. Thus, the description pointed to by the Examiner is not a composition of an encapsulated *modified* allergen. It is *not* a "pharmaceutical composition" as recited in the present claims.

The '978 publication does mention that modified allergens can be produced "recombinantly" (page 25, lines 3-12). However, it does not describe such production, nor does it even specify that "recombinant production" necessarily means "production in cells." Even if "recombinant production" were assumed to mean "production in cells," the description certainly does not describe what kind of cells would be used. A mere mention that modified allergens can be produced recombinantly in some way, cannot constitute a description of a composition including (1) dead (2) *E. coli* (3) encapsulating modified peanut allergens, as recited in the present claims, let alone of a pharmaceutical composition.

Furthermore, the Examiner's argument that the '978 publication describes "encapsulation" within dead *E. coli* is based on a comment at page 16, lines 30-32 of the '978 publication that urea was utilized during isolation of the expressed *wild type* proteins. The Examiner concludes from this comment that urea solubilization (1) would be used if modified proteins were utilized; (2) is required; and (3) means that the expressed protein was in inclusion bodies, and therefore "encapsulated" within the cells. There is no basis for any of these conclusions.

First, as established above, this portion of the specification relates only to wild type allergens and says nothing at all about the behavior of *modified* allergens when expressed in cells. Furthermore, Applicant submits that the '978 publication does not disclose that the cells expressing wild type allergens *must* be solubilized with urea; it merely states that these cells in this experiment *were* solubilized with urea. Therefore, the wild type allergen is *not necessarily* expressed in inclusion bodies. Regardless, treatment of cell extracts with urea during protein purification is a standard technique that is often used by those of skill in the art whether a protein is expressed in inclusion bodies or not. The mere mention that urea was utilized does not and cannot constitute a description of any allergen being encapsulated within dead *E. coli.* Furthermore, as discussed above, the specification is completely silent as to whether urea is even used at all during purification of *modified* allergens. For all of the reasons outlined above,

Applicant submits that the Examiner's conclusion that the modified allergen of '978 is located in the cytoplasm of *E. coli* cells is ill-founded and improper.

The Examiner further states that the claimed invention differs from the teachings of the '978 reference *only in that* the composition comprising modified allergen encapsulated in *E. coli* (1) comprises *E. coli* that is dead is instead of alive, and (2) that the *E. coli* was killed by heat. The Examiner cites Fenton *et al.* and Vrtala *et al.* as remedying the deficiencies of the '978 reference. As established above, and in contrast to the Examiner's position, the '978 reference differs from the present claims because the '978 reference does not teach a modified allergen encapsulated in *E. coli*. For this reason and for reasons discussed below, Applicant submits that Fenton *et al.* and Vrtala *et al.* do not remedy the defects of the '978 reference.

As an initial matter, Applicant points out that the Examiner has not identified any motivation for one of ordinary skill to modify the teachings of the '978 application to achieve encapsulation of (1) a modified allergen; in (2) dead *E. coli* that were (3) killed by heat. Even if there were such motivation, Applicant submits that a person of ordinary skill would not look to Fenton *et al.* for helpful teachings because, among other things, the compositions and methods described in Fenton *et al.* result in a *mutation-specific immune response.* Fenton *et al.* teach a pharmaceutical composition comprising dead *E. coli* that express a particular modified Ras protein. Subjects immunized with any given Ras mutant develop immunity *only* to that particular Ras mutant and do not develop immunity to wild type Ras or any other mutant forms of Ras. Fenton *et al.* describe "lytic activity of Ras-immunized T cells only against tumor cells expressing the same mutant form of Ras used in the immunizations" (page 1859, column 1) and "proliferation of Ras-immune T cells in response to the appropriate mutant Ras peptides but not to wild-type or other mutant Ras peptides" (page 1859, column 2). Fenton *et al.* further state that "The immunization methods described here likely select for T-cell responses limited to the mutated epitope, since tolerance to wild-type ras sequences (expressed in virtually all cells of the body) would be expected to significantly dampen the response to these sequences as potentially immunogenic epitopes" (page 1860, column 1, first paragraph).

In contrast, the '978 publication is directed to the development of compositions containing modified allergens that will be used to immunize a subject *against different allergens* (*i.e.*, against wild type allergens). Thus, Applicant submits that one of ordinary skill in the art would *never* look to Fenton *et al.* for guidance in modifying the teachings of the '978 publication

because the compositions and methods of Fenton *et al.* yielded a result that is opposite to the goals of the '978 publication. Applicant, therefore, respectfully submits that Fenton *et al.* cannot be properly combined with the '978 publication to formulate a § 103 rejection over the present claims.

Furthermore, Applicant points out that Fenton *et al.*, in fact, *teaches away* from immunization using cells comprising *modified* allergens. Considering that the compositions and methods of Fenton *et al.* are useful for generating a *mutation-specific immune response*, Fenton *et al.* teaches away from the possibility that immunization with a particular modified allergen can result in protective immunity against wild type allergens or other modified allergens other than the particular one that was used to immunize the individual. One of ordinary skill in the art looking at Fenton *et al.* would certainly conclude that immunizing an individual with a modified allergen would not result in protective immunity against multiple variants of that allergen (*e.g.*, wild type allergen, other modified allergens). In contrast, the present inventors have described and reduced to practice administration of a modified allergen to an individual in order to immunize the individual against wild type allergen and/or other modified allergen variants.

For all of these reasons, Applicant respectfully submits that Fenton *et al.* does not remedy any of the defects of the '978 reference.

The Examiner states that Vrtala *et al.* teach feeding of recombinant attenuated *Salmonella* that express modified birch pollen allergens to mice in order to immunize mice against birch pollen allergens. As acknowledged by the Examiner, Vrtala *et al.* teach *live Salmonella*, whereas the present claims are drawn to *dead E. coli*. The Examiner states that it would have been obvious to use the dead *E. coli* of Fenton *et al.* to overcome the technical and ethical problems associated with using live allergy vaccines of Vrtala *et al.* Applicant respectfully disagrees.

Vrtala *et al.* acknowledge and extensively discuss the technical and ethical problems associated with use of live allergy vaccines. Vrtala *et al.* offer *one possible solution* to overcoming these problems, which is to attenuate the live bacteria (*e.g.*, by making a mutation that renders the bacterium less pathogenic or non-pathogenic). Vrtala *et al.* do not even mention the possibility of using dead bacteria as vaccines. The fact that Vrtala *et al.* (1) acknowledge and discuss the problem with live vaccines and (2) offer a solution indicate that Vrtala *et al.*, in fact, *teach away* from any other kind of solution, such as the use of dead *E. coli* as recited in the present claims. Therefore, one of ordinary skill in the art reading Vrtala *et al.*, in light of the

teaching away of Vrtala *et al.*, would not be led to Fenton *et al.* and would not be guided to utilize dead *E. coli*, as recited in the present claims.

Given that each of Fenton *et al.* and Vrtala *et al.* teach away from aspects of the present claims, there can be no combination of Fenton *et al.* and Vrtala *et al.* with each other and/or with the '978 publication that renders the present claims obvious. Applicant, therefore, respectfully requests that the rejection be removed.

The Examiner has rejected claims 34 and 41 under 35 U.S.C. § 103 as being unpatentable over the '978 publication in view of Leclerc *et al.* (1990, *J. Immunol.*, 144(8):3174-3182) and Vrtala *et al.* This rejection is respectfully traversed; reconsideration and withdrawal is requested.

As discussed above, the fact that Vrtala *et al.* (1) acknowledge and discuss problems associated with use of live vaccines and (2) offer a solution to these problems indicate that Vrtala *et al.*, in fact, *teach away* from any other kind of solution, such as the use of dead *E. coli* as recited in the present claims. The Examiner cites Leclerc *et al.* for (1) its use of dead *E.* coli and (2) its description of a modified allergen located in the periplasm instead of the cytoplasm. As discussed above with respect to the combination of Vrtala *et al.* and Fenton *et al.*, the teachings of Vrtala *et al.* are inconsistent with any disclosure teaching the use of dead cells. Thus, the teachings of Vrtala *et al.* are inconsistent with the teachings of Leclerc *et al.* Applicant submits that, in light of the teaching away of Vrtala *et al.*, one of ordinary skill in the art reading Vrtala *et al.* would not be led to Leclerc *et al.* and would not be guided utilize dead *E. coli*, as recited in the present claims. Applicant, therefore, respectfully requests that the rejection be removed.

The Examiner has rejected claims 44-45 under 35 U.S.C. § 103 as being unpatentable over the '978 publication in view of Fenton *et al.* and Vrtala *et al.* and further in view of WO 92/14487 ("the '487 publication") and U.S. patent 6,270,723 ("the '723 patent") further in view of WO 92/14487 and U.S. Patent 6,270,723. This rejection is respectfully traversed; reconsideration and withdrawal is requested.

The Examiner cites the '487 publication and the '723 patent for teaching methods of killing *E. coli* using chemical treatments, such as alcohol, bleach, or pressure sterilization. As discussed above, the '978 publication in view of Fenton *et al.* and Vrtala *et al.* does not render obvious the claimed compositions of the present application. Applicant submits that the

deficiencies of '978 publication in view of Fenton *et al.* and Vrtala *et al.* exist no matter whether the *E. coli* are killed by heat treatment or by chemical treatment. Therefore, inclusion of the '487 publication and the '723 patent in the rejection does not overcome the deficiencies of '978 publication in view of Fenton *et al.* and Vrtala *et al.* Applicant, therefore, respectfully requests that the rejection be removed.

Double patenting

Claims 34-36 and 38-47 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 34-45 of co-pending Application No. 10/728,051. Applicant respectfully defers further comment on this rejection until the claims of either application have been found to be patentable.

Conclusion

Applicant, therefore, respectfully submits that the present case is in condition for allowance. A Notice to that effect is respectfully requested.

If, at any time, it appears that a phone discussion would be helpful, the undersigned would greatly appreciate the opportunity to discuss such issues at the Examiner's convenience. The undersigned can be contacted at (617) 248-5175.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

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